The Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet): Surveillance Methodology

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BACKGROUND: This report focuses on the common protocol developed by the Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet) for population-based surveillance of Duchenne and Becker muscular dystrophy (DBMD) among 4 states (Arizona, Colorado, Iowa, and New York). **METHODS:** The network sites have developed a case definition and surveillance protocol along with software applications for medical record abstraction, clinical review, and pooled data. Neuromuscular specialists at each site review the pooled data to determine if a case meets the case criteria. Sources of potential cases of DBMD include neuromuscular specialty clinics, service sites for children with special healthcare needs, and hospital discharge databases. Each site also adheres to a common information assurance protocol. **RESULTS:** A population-based surveillance system for DBMD was created and implemented in participating states. **CONCLUSIONS:** The development and implementation of the population-based system will allow for the collection of information that is intended to provide a greater understanding of DBMD prevalence and health outcomes. *Birth Defects Research (Part A) 76:793–797, 2006.* © 2006 Wiley-Liss, Inc.

Key words: muscular dystrophy; surveillance; prevalence; health outcomes

INTRODUCTION

Muscular dystrophy refers to a group of genetic disorders characterized by progressive muscle weakness. Duchenne and Becker muscular dystrophy (DBMD) are allelic X-linked conditions that are the most common muscular dystrophies in children. Estimates from newborn screening (Greenberg et al., 1991; Bradley et al., 1993; Van Ommen and Scheuerbrandt, 1993; Drousiotou et al., 1998) and preschool developmental screening (Takeshita et al., 1987) programs as well as clinic-based programs (Hauser et al., 1993; Mostacciuolo et al., 1993;

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Ballo et al., 1994; Peterlin et al., 1997; Darin and Tulinius, 2000; Chung et al., 2003) suggest that DBMD affects about 1 in 3500 to 1 in 6000 male births.

Population-based surveillance of DBMD is needed to establish prevalence estimates in different racial and ethnic groups in the United States. In addition, the identified cohort can provide the basis for population-based studies of secondary conditions, treatment use and impact, and other public health issues. State birth defects surveillance programs in the United States typically do not ascertain children with DBMD because they are not symptomatic at birth. Consequently, existing birth defects surveillance programs would require modification to accomplish population-based assessments of the impact of DBMD in states. The Centers for Disease Control and Prevention (CDC) awarded 4 cooperative agreements in 2002 to programs in Arizona, Colorado, Iowa, and New York, and another in 2005 to Georgia to develop and implement common protocols for DBMD case ascertainment, long-term follow-up, and research. This report focuses on the common protocol developed for population-based surveillance of DBMD among the initial awardees.

MATERIALS AND METHODS

Population Description

Geographically, the areas under surveillance are the states of Arizona, Colorado, Iowa, and a 12-county area in western New York. The population under surveillance includes residents in these areas born on or after January 1, 1982. This birth date was based on the availability of clinic records in the major clinics serving these individuals in each area and the identification of dystrophin as the causative gene for DBMD in 1987, ushering in the modern era of diagnosis (Koenig et al., 1987). Using an average of 5 years of age for disease onset, for each year from 1987 to 2004, a point prevalence and birth cohort prevalence will be determined. A lifetime residential history of patients will be collected to monitor the mobility of subjects in and out of each site's catchment area. Using the birth populations of each area included in surveillance for the years 1982 to 2003, 2,284,852 male births are included in the surveillance population (71% white, non-Hispanic; 5% African American, non-Hispanic; 18% Hispanic; and 6% other, non-Hispanic).

Sources and Case Finding

The Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet), like other public health surveillance programs for birth defects and developmental disabilities, examines source records rather than children. It relies on clinicians to recognize, diagnose, and document DBMD and to record relevant epidemiological, medical, and other findings. Not all relevant diagnostic criteria and data may be found in any single record or source of referral. Therefore, MD STARnet uses a multiple source approach.

The case-finding methodology used by MD STARnet is based on active record review of source records. In Colorado, DBMD is reportable by board of health regulation to the state health department by physicians and other health care providers, and by hospitals and other health care facilities. In Iowa, state law authorizes the Iowa Registry for Congenital and Inherited Disorders to access hospital records, physician records, clinical charts, vital records, and other medical information of patients with DBMD to conduct DBMD surveillance. In New York, by regulation, DBMD is reportable to the New York Congenital Malformations Registry, but only up to age 2 years. However, the State Department of Health, under existing public health law allowing the Commissioner to perform studies, is able to access information on cases up to age 21 years. In Arizona, DBMD reporting is not mandatory.

Building on existing resources and collaborations, each MD STARnet site identified the major sources for conducting surveillance activities. These sources include neuromuscular clinics, hospitals and hospital discharge databases, private physicians, service sites for children with special health care needs, and birth defect surveillance programs. In addition, each state links patients identified to birth and death certificate data and will implement a National Death Index search for more complete ascertainment of deaths among cohort members.

Methods used to identify potential DBMD cases include: 1) identification of individuals with an ICD-9 code of 359.1 (hereditary progressive muscular dystrophy, muscular dystrophy: NOS, distal, Duchenne, Erb's, facioscapulohumeral, Gower's, Landouzy-Dejerine, limb-girdle, ocular, oculopharyngeal) in hospital discharge records; and 2) identification of possible cases in specialty clinics through reference to logs and registries. In addition, local Muscular Dystrophy Association (MDA) representatives cooperated in advertising of the project and encouraging recruitment of families through self-reporting.

Surveillance Case Definition

The MD STARnet cohort includes individuals who meet the criteria for case abstraction and are treated for muscle weakness by age 21 years or have laboratory findings that provide a very high probability that they will develop muscle weakness by age 21 years. The MD STARnet case definition does not distinguish between those with Duchenne and Becker muscular dystrophy, as these allelic conditions form a spectrum of clinical severity and cannot be distinguished from one another by either laboratory or clinical criteria in all cases. Clinical and family history criteria determine whether the abstracted records meet 1 of the case definition categories shown in Table 1. To qualify for any of the case definition categories other than the asymptomatic category, individuals must have any 1 of 14 different symptoms referable to a dystrophinopathy, such as progressive muscle weakness or positive Gower's sign. The gradation from possible to probable to definite in the case definition categories reflects documentation of laboratory and family history information that is increasingly specific for a dystrophinopathy. Individuals in the asymptomatic category are those who have met confirmatory laboratory and/or family history criteria, but who have not yet developed clinical symptoms. Such persons are most commonly male siblings of individuals in the definite category or males related to individuals in the definite category through carrier females.

Table 1
MD STARnet Case Status Definitions

Case status	Symptoms[a]		Criteria
Definite	Yes	AND	Documented dystrophin mutation OR Muscle biopsy showing abnormality of dystrophin with no alternative explanation identified OR Elevated CK, pedigree compatible with X-linked inheritance and an affected family member with dystrophin mutation or dystrophin abnormality on muscle biopsy
Probable	Yes	AND	Elevated CK level and an X-linked pedigree consistent with a dystrophinopathy
Possible	Yes	AND	Elevated CK level
Asymptomatic	No	AND	Documented dystrophin mutation OR Muscle biopsy showing abnormality of dystrophin with no alternative explanation identified OR Elevated CK, pedigree compatible with X-linked inheritance and an affected family member with dystrophin mutation or dystrophin abnormality on muscle biopsy
Affected female	Yes	AND	Positive dystrophin mutation analysis OR Positive muscle biopsy for abnormal dystrophin

[a] Symptoms related to a dystrophinopathy.
CK, creatine kinase.

Surveillance Data Collection Tools, Standards, and Resources

Surveillance data collection includes a baseline abstract to determine diagnostic eligibility and annual follow-up abstracts. Follow-up abstracts are conducted until the child is deceased or has residence outside of a site catchment area in order to establish disease progression and occurrence of complications for each identified patient. Data collected include demographic and diagnostic information as well as medical and family history of muscular dystrophy for the index cases and demographic information for the primary caregivers (e.g., biologic parents) and primary care providers for each index case. Surveillance data abstracted at each project site are edited, stripped of identifiers, and transmitted to the MD STARnet Data Coordinating Center (DCC). A Clinical Review Committee (CRC), comprised of 1 neuromuscular clinician at each site, conducts a blind review of selected diagnostic variables for each patient and assigns each patient to 1 of the surveillance case definition categories. Unanimous agreement of all 4 sites is required. Discrepancies are resolved in a monthly conference call with a full committee review of all non-unanimous cases. Final assignment for each patient is compiled by the DCC and then communicated to the respective project site.

The DCC, located at the University of Iowa, developed an electronic software suite of surveillance data collection tools (available upon request). The software suite developed by the DCC includes Abstraction, Clinical Review, File Transfer, and Aggregate Report applications in Microsoft Access (Microsoft, Redmond, WA). Associated with these applications are Abstraction, Clinical Review Application, Pooled Clinical Review, and Clinical Review Tracking databases in Microsoft Access, and a Pooled Abstract database in Oracle (Oracle, Redwood Shores, CA). The DCC also hosts the MD STARnet web site and file transfer protocol (ftp) site.

The MD STARnet data description documents were used as the basis for designing the variables and tables in the Abstraction database. The application was refined over several iterations in close consultation with abstractors, data managers, clinicians, and principal investigators at each participating site. The current version of the application is set up to accommodate annual follow-up abstraction of previously abstracted cases.

In order to protect against unauthorized access of potentially sensitive information, security is built into the project at the network, software, and application levels. Users need an ID and password and must be members of the MD STARnet workgroup in order to be able to access the application. User permissions are determined by their role in the project. A total of 5 roles were defined: 1) Data Manager with administrative privileges, capable of entering, editing, and viewing data and modifying the database; 2) Abstractor, who can enter, edit, and view data but not change the database structure; 3) Local Reviewer, who can only edit and view data; 4) Investigator, who can only view data; and 5) Clinical Reviewer, who can only access the Clinical Review application. Each user sees a different menu based on his or her role as he or she uses the application. In addition, sites are recommended to use encryption software to provide an additional layer of security for the database.

The Clinical Review Application is used by members of the CRC to determine the case definition category of the abstracted case. The monthly review sequence starts with the sites sending the pooled database to the DCC. The data to be reviewed are compiled and loaded into the Clinical Review Application and uploaded via ftp to each site for clinical review. Each case is assigned a case status and the clinicians return the reviewed Clinical Review Application to the DCC. The DCC compiles a list of discrepant case assignments that are resolved, as described above. The DCC then sends a report to each site with the case definition category for the cases from that site.

The MD STARnet web site is used as a communication channel for members of the project and for all the applications mentioned above. The website is password-pro-

tected to allow access only to authorized MD STARnet personnel. It functions as a repository of project plans, contact information, meeting minutes, monthly calendars, and other project-related information. It is also the distribution point for releases of new versions of software applications and associated instruction manuals, and the collection point for change requests and monthly Clinical Review Application databases.

The Aggregate Report application is run monthly to generate monthly reports of case status counts to track the progress of the cases through the review process and to track the number of cases identified in each case definition category. The Pooled Abstract database, developed in Oracle, stores centrally deidentified data from all abstracted records for which review is complete.

MD STARnet has also developed an Information Assurance Policies and Guidelines document (available upon request) that describes the administrative safeguards, physical and personnel security measures, technical security measures that are built into the databases and data collection applications, and organizational compliance policies. Tailored explicitly for MD STARnet, these procedures ensure confidentiality of protected data elements and preserve the privacy of study participants.

At each site, surveillance activities are conducted by 1 to 2 abstractors, a data manager, and a program manager, with oversight from a project director and input from a clinician familiar with DBMD.

Surveillance Evaluation

To assure the quality of the abstraction methods, we conducted abstractor training prior to initiating record review, and plan to conduct an interabstractor reliability assessment. In this assessment, abstractors will reabstract 5 common deidentified medical records submitted from participating sites. Abstracted data from each abstractor at each site will be compared with all other abstractors, and the agreement between abstractors on selected data variables will be measured. An onsite evaluation at each site will also be conducted to assure that similar processes are followed at each site. To assess completeness, a capture-recapture analysis is planned.

RESULTS

A total of 588 cases were abstracted. Of these, 83 (14.1%) were excluded, either because they did not meet birth or residency requirements or because they clearly had a condition other than DBMD, and 432 (73.5%) have been sent to the CRC for case definition assignment. The remaining cases (12.5%) are under local review. Full results will be presented in future reports.

DISCUSSION

A total of 4 states with existing birth defects surveillance programs participate in MD STARnet, a population-based surveillance project to identify children with DBMD. A fifth state has recently been added. Previously, these programs did not routinely ascertain DBMD conditions, with their traditional emphasis on structural birth defects identified during a child's first year of life. The diagnosis of DBMD is typically made when the child is 4 or 5 years of age (Mohamed et al., 2000), which would have required these systems to expand their age limit and add new conditions for DBMD. The experiences of surveillance programs for fetal alcohol syndrome (Hymbaugh et al., 2002) and autism surveillance (Rice et al., 2004), which also require additional sources and expanded age limits, guided the development of the MD STARnet methods. There is a range of integration with the existing birth defects surveillance programs in the 4 states. In Arizona, there is no integration, as MD STARnet is operated in an academic setting, and the birth defects program is operated from Arizona's health department. In New York, both programs are operated from New York's health department, though there is no additional integration. In Colorado and Iowa there is fuller integration, including statistical analysis, data management, and programmatic functions. Abstracting functions are also integrated in Iowa.

The MD STARnet methodology is similar, in general, to the approach many birth defects surveillance systems use. However, the surveillance of DBMD involves special challenges that do not pertain to traditional birth defects surveillance systems. As a result of changes in technology, MD STARnet has encountered major challenges in devising a case definition that applies to all boys with DBMD in the surveillance system. The diagnostic testing technology for DBMD has changed considerably over the duration of the study period, so that older individuals have infrequently undergone genotyping or immunohistochemical staining for dystrophin by muscle biopsy and are therefore unlikely to meet the definite case definition criteria. Even when the most up-to-date technology for clinical diagnostic of DBMD is used, there are additional challenges, since a substantial proportion of affected individuals do not demonstrate either a deletion or duplication of the dystrophin gene; and muscle biopsies may not undergo a sufficiently rigorous analysis that will distinguish DBMD conclusively from other muscular dystrophies. And finally, because the diagnosis of DBMD may not be made until school age or later, it may be difficult to derive accurate prevalence estimates for more recent years.

At present, there are no widely agreed upon standards of care for DBMD, so specific treatment for DBMD is an area of active research. Most information currently available is restricted to voluntary participants or to individuals who attend a specific clinic; samples not necessarily representative of the entire DBMD population. To help address this gap, MD STARnet will collect population-based data on the source, frequency, and type of preventive and medical care among persons with DBMD. These data can be used to assess the relationship between specific care patterns and outcomes, such as age at first wheelchair use, and can assist in the development of care standards for DBMD. Additional information about the initial symptoms of DBMD, the diagnostic ''odyssey'' experiences prior to a diagnosis of DBMD, treatments received, the course of disease, family structure, and potential barriers to receipt of care will be collected via yearly interviews with family members.

There are limitations to MD STARnet. One is the diagnostic issue discussed above. Also, although we will include all known places or institutions at which individuals with DBMD are diagnosed or cared for, some individuals may still be missed. Finally, this surveillance system is designed to identify only those patients with Duchenne or Becker muscular dystrophy identified by

the age of 21 years, so those identified at an older age will be excluded. Despite these limitations, MD STARnet, the only multistate surveillance system in the United States focused on DBMD, is expected to contribute important new epidemiologic and health outcome information about childhood onset dystrophinopathies.

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